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A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS)

The Definition of Remission in SLE (DORIS) task force

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Abstract

Objectives. Treat-to-target recommendations have identified ‘remission’ as a target in systemic lupus erythematosus (SLE) but recognize that there is no universally accepted definition for this. Therefore, we initiated a process to achieve consensus on potential definitions for remission in SLE.

Methods. An international task force of sixty specialists and patient representatives participated in preparatory exercises, a face-to-face meeting, and follow-up electronic voting. The level for agreement was set at 90%.

Results.

The task force agreed on eight key statements regarding remission in SLE and three principles to guide the further development of remission definitions:

1. Definitions of remission will be worded as follows: *Remission in SLE is a durable state characterized by* (reference to symptoms, signs, routine labs).
2. For defining remission a validated index must be used, e.g., clinical-SLEDAI = 0, BILAG2004 D/E only, clinical ECLAM =0; with routine laboratory assessments included, and supplemented with Physician Global Assessment.
3. Distinction is made between remission off and on therapy: *Remission-off-therapy* requires the patient to be on no other treatment for SLE than maintenance antimalarials; and *Remission-on-therapy* allows patients to be on stable maintenance antimalarials, low-dose corticosteroids (prednisone ≤ 5 mg/d), maintenance immunosuppressives and/or maintenance biologics.

The task force also agreed that the most appropriate outcomes (dependent variables) for testing the prognostic value (construct validity) of potential remission definitions are: Death, Damage, Flares, and measures of Health-related quality of life.

Conclusion. The work of this international task force provides a framework for testing different definitions of remission against longer-term outcomes.

Introduction

Outcomes in systemic lupus erythematosus (SLE) have improved considerably over the past decades. For the most widely studied specific organ involvement in SLE, lupus nephritis, results from clinical trial follow-up studies demonstrate that the long-term renal survival in this condition has now improved to greater than 90%.[1] However, not all outcomes in SLE show the same favorable trends. Most notably the overall health-related quality of life (HR-QoL) for patients with SLE remains reduced.[2]. This and other considerations prompted the initiation of the Treat-to-Target for SLE (T2T/SLE), initiative which over the past several years established an international consensus on the approach to the therapy of SLE based on 1) identifying an appropriate target for each patient; 2) initiating treatment steps to try to achieve this target; 3) assessing the target; and 4) adjusting the therapeutic approach, if necessary. These elaborations led to the T2T/SLE recommendations published in 2014.[3] One of the most significant targets in SLE was identified as “remission of systemic symptoms and organ manifestations”. However, it was recognized by the panel that no generally accepted definition of remission in SLE exists today. Such a definition could be important for basic, clinical and epidemiological studies and clinical trials in lupus, but also for clinical practice. The literature on this topic demonstrates that many clinical trials and observational studies have used a large number of different *ad hoc* definitions of remission; many of these were reviewed in a recent study.[4] Consequently, the T2T/SLE panel identified the definition of remission as a research priority for SLE. In response, an initiative was undertaken in order to achieve consensus in a large multiparty international task force on potential definitions of remission in SLE (DORIS).

Methods

An international task force consisting of rheumatologists, nephrologists, dermatologists, clinical immunologists and patient representatives, totaling 60 individuals, was convened. In March 2014, a

preliminary meeting was held by a steering committee consisting of 15 of these representatives. The steering committee identified four domains critical to further development of remission definitions; ten preliminary statements regarding remission that were felt to be uncontroversial; key controversies; and a set of proposed topics for further discussion. During the following 4-month period, the ten preliminary statements were presented to the full task force electronically, deliberated upon by email, and then subjected to formal electronic voting. High-level agreement was readily achieved for eight of these, whereas two were placed on the agenda for the subsequent consensus conference. Moreover, an additional number of key topics were identified during these deliberations that were to be dealt with more thoroughly at the face-to-face meeting.

In August 2014, a consensus conference took place where a large majority of the full task force was present. The explicit goal of this consensus conference was to establish guiding principles for working towards a definition of remission in SLE and to formulate proposed definitions that would be amenable to scientific testing. During this meeting, formal votes were taken on a range of points. The level for agreement was set at >90%.

The procedure was informed by the results of the systematic literature review that was carried out in the context of the ‘Treat-to-target in SLE’ project [3] and was modified and updated in September 2015. We focused on two of the twelve original topics of interest that were more relevant to the present study, namely topic #2 (*“Have any definitions for low disease activity and remission, -both global and organ-specific-, been validated as surrogates of therapeutic success against damage accrual, mortality, and QoL in SLE?”*) and topic #5 (*“Is sustained reduction of disease activity or prevention of flares, -both general and organ-specific-, an achievable goal in SLE?”*).[3] The literature search was repeated in September 2015 by author GB to include more recently published literature. The PubMed database was searched using index terms and all English-language human studies were evaluated based on the title, abstract and/or full-text. For the purpose of the present

study, we report on the systematic literature review results relevant to remission only, which were published since the year 1990 and included ≥ 70 SLE patients.

Results

Domains considered critical for defining remission in SLE. Four domains critical for defining remission in SLE were identified: clinical disease activity, serological activity, duration, and treatment. Within each of these domains a number of key issues were identified and these form the basis of the work described here.

Preliminary statements on remission in SLE.

Ten statements, considered highly relevant for developing a definition of remission and expected to be uncontroversial, were prepared by the steering committee and subjected to electronic voting by the task force. Eight of these statements readily achieved a high level of consensus ($>90\%$) and are shown in **table 1**.

	Statement	% in favor
1	Remission is a desirable outcome for the patient with SLE	100%
2	Remission in SLE includes, at the very least, the absence of symptoms and signs of SLE.	100%
3	Remission in SLE is <u>not</u> the same as a cure.	100%
4	Remission in SLE is <u>not</u> the same as low disease activity.	93%
5	Remission is a state that, if sustained, is associated with a low likelihood of adverse outcome.	100%
6	“Serological activity” in SLE generally refers to the presence of	100%

	anti-DNA antibodies and/or hypocomplementemia.	
7	Treatment with antimalarials <u>does not</u> preclude the patient from being considered to be in remission.	98%
8	Treatment with moderate- or high-dose steroids <u>does</u> preclude the patient from being considered in remission.	98%

Table 1. Preliminary statements on remission in SLE. Out of ten statements selected by the steering committee, eight achieved >90% agreement on electronic voting by the entire task force. Two statements (“A definition of remission SLE must be reasonably consistent with the use of this term in the literature” and “Durability in time can be added to any definition of remission in order to define a ‘durable remission’ but need not be included in the definition of remission itself”) did not achieve consensus and were discussed further at the face-to-face meeting.

Therefore, remission is identified as a desirable outcome for patients with SLE with, -at the very least-, the absence of major symptoms and signs of SLE. Remission is conceived of in terms different from a cure, yet it is also regarded as meaningfully different from a low disease activity state, including the lupus low disease activity state (LLDAS) that has recently been proposed by the Asia-Pacific Lupus Collaboration.[5] Perhaps most critically for future work in this area, it is recognized that remission, like LLDAS, has to be a state that, if sustained, is associated with a low likelihood of adverse outcome. To this end, the systematic literature review identified a number of observational studies in patients with lupus nephritis, which illustrate that attainment of (complete) *renal remission* (or response) (typically defined as a very low level of proteinuria, with normal or stable renal function, with or without inactive urine sediment) is associated with favorable long-term patient and renal outcomes (**Table 2**). Similarly, in general SLE, three retrospective cohort studies

have suggested that patients who achieve disease remission have significantly lower rates of damage accrual or mortality after follow-up.

Author (ref.)	N	Remission definition(s)	Remission achieved (%)	Association of remission with outcomes
General SLE				
Drenkard [6]	667	≥1 year of clinically inactive disease (serological activity allowed) that permitted withdrawal of all lupus drugs	23.4%	12.5-fold reduced risk for death (follow-up 11.6 ± 6.0 years), after controlling for effects of renal disease and thrombocytopenia
Nossent [7]	200	Physician judgment (not otherwise specified), assessed during the first year of disease	27.5%	Lower annual relapse rates, lower average SLEDAI, lower cumulative SDI scores at the end of 5-year follow-up
Zen [8]	224	≥5 years complete remission with SLEDAI-2K=0 (HCQ allowed) or clinical remission with clinical SLEDAI-2K=0 (serological activity allowed) off-steroids or on low-dose steroids (HCQ/ISTs allowed)	7.1% (complete remission), 14.7% (off-steroids), 15.6% (on steroids)	Damage accrual rates (end of 5-year follow-up): 18.8% (complete remission), 18.2% (off-steroids), 37.1% (on steroids), and 51.4% (no remission)
Medina-Quiñones [9]	532	≥3 years with BILAG C, D or E, no serological activity, off-steroids, off-immunosuppressives (HCQ/NSAIDs allowed)	14.5%	Lower mortality rates (5.2% vs. 13.4%; median follow-up 12 years)

Lupus nephritis

Moroni [10]	70	CRR: UPr* <0.2, normal renal function	38.5% (at last follow-up)	CRR was associated with fewer renal flares, better outcome of renal flares
Mok [11]	183	CRR: UPr <0.3, normal SAlb, normal renal function, assessed at the end of first year of therapy	64%	Lack of CRR was associated (RR 9.9) with development of ESRD (mean follow-up 181 months)
Korbet [12]	86	CRR: SCr ≤1.4 mg/dl, UPr ≤0.33, attained within 5 years of entering the study. See also refs [13], [14]	43%	CRR was associated with reduced risk of progression to ESRD (HR 0.12), increased rates of patient survival at 5 and 10 years (follow-up 120 ± 65 months)
Illei [15]	145	CRR: SCr <130% of the lowest level during treatment, UPr <1, inactive urine sediment, off IST (HCQ and prednisone ≤10 mg/day allowed), for ≥6 months	50.3%	Lack of CRR was associated with increased risk for severe nephritic flare (LR 5.7) and progression to ESRD (LR 7.0) (median follow-up 116 to 123 months)
Hill [16]	71	CRR: SCr ≤123 μmol/L, UPr ≤0.33	N/D	Lack of CRR was associated with decreased 10-year survival rates from doubling of SCr
Mok [17]	189	CRR: stabilized/improved SCr, UPr <1, improved	55%	Lack of CRR was associated with increased risk (HR

		serum C3 for ≥ 6 months, assessed at the end of IST		4.5) for development of ESRD (mean follow-up 96.5 months)
Mok [18]	268	Same as in [17]	59%	Lack of CRR was associated with increased risk (HR 4.5) for adverse outcome (doubling of SCr or ESRD or patient death)
Moroni [19]	93	CRR: SCr <1.2 mg/dL, stable or 25% increase of baseline CrCl, UPr <0.2, inactive urine sediment	82% (63.4% at last follow-up)	Lack of CRR was associated (RR 4.3) with development of chronic renal insufficiency (median follow-up 181 months)
Mak [20]	149	CRR: stabilized/improved SCr, improved serum complement, UPr <1, inactive urine sediment for ≥ 6 months, assessed at the end of first year of therapy	60.4%	Lack of CRR was associated with renal damage (mean follow-up 80 months)
Lee [21]	77	CRR: SCr <1.2 mg/dl, UPr <0.2, inactive urinary sediment, for ≥ 6 months	52%	Lack of CRR was associated with development of chronic renal insufficiency and/or death (follow-up 8.3 ± 4.4 years)
Sun [22]	100	CRR: UPr ≤ 0.4 , normal urinary sediment, normal SAlb, normal SCr	58%	Lack of CRR was associated with ESRD (median follow-up 60 months)
Ayodele	105	CRR: stable [$\pm 25\%$] renal function, UPr <0.2,	44.8%	CRR was associated with higher mean survival time

[23]		assessed at the end of first year of therapy			
So [24]	117	CRR: SCr ≤ 1.4 mg/dl, UPr ≤ 0.5 , inactive urine sediment, assessed after 6 months of therapy	50.4%		CRR was associated with reduced risk for subsequent renal flares and chronic renal failure (mean follow-up 66–76 months)
Reich [25]	98	CRR: SCr ≤ 120 mmol/l (1.4 mg/dl), UPr < 0.3	74.5%		Lack of CRR was associated with faster GFR decline (follow-up 12.4 ± 8.4 years)
Alsuwaida [26]	77	CRR: SCr ≤ 125 μ mol/L, UPr ≤ 0.33	41.6%		CRR was associated with higher renal survival rate at 10 years. Lower risk for doubling of SCr
Dhir [27]	188	UPr reduction by $\geq 50\%$ to < 2 , inactive urine sediment, normal SCr (≤ 1.5 mg/dl), assessed at the end of first year	54.6% [§]		Lack of remission was associated (HR 13.8) with chronic renal failure or death (median follow-up 6 years)
Moroni [28]	103	CRR: SCr < 1.2 mg/dL, stable or 25% increase of baseline CrCl, UPr < 0.2 , inactive urine sediment	70.9%		CRR was associated with good renal outcome (no chronic renal insufficiency) (follow-up 156 ± 105 months)
Mahmoud [29]	135	CRR: SCr ≤ 1.2 mg/dl, and 25% increase of baseline CrCl if abnormal, or stable value if abnormal at	59.3%		Lack of CRR in the first year was associated with adverse outcome (death, ESRD or doubling of SCr)

		baseline, UPr <0.2, inactive urine sediment		
Fernandes das Neves [30]	105	CRR: UPr <0.2, negative anti-dsDNA antibodies, normal C3, and normal SCr, for ≥ 5 consecutive years	38.1%	CRR was associated with preservation of normal renal function (80% vs. 43%) and reduced mortality (0% vs. 22%) compared to partial/no remission group (follow-up 13.7 ± 14.1 years)
Koo [31]	193	CRR: UPr <0.3, for ≥ 6 months	42.5%	CRR was associated with reduced risk of mortality and ESRD (follow-up 158 ± 70 months)
Dall'Era [32]	76	Different sets of response criteria based on a range of cut-offs of UPr, SCr, and RBCs at 3, 6, and 12 months. Best criterion was UPr <0.8 at 12 months	59.2%	Sensitivity 81% and specificity 78% for favorable long-term (7 years) renal outcome ($\text{SCr} \leq 1.0$ mg/dl). The LUNAR study remission criterion ($\text{UPr} \leq 0.5$, SCr $\pm 15\%$ of baseline, inactive urine sediment) had 32% sensitivity, 91% specificity
Tamirou [33]	104	Different sets of CR criteria based on levels of UPr, Scr, and urinary RBCs at 3, 6, and 12 months. Best criterion was $\text{UPr} \leq 0.5$ at 12 months	49.0%	Positive predictive value 92% for achieving good long-term renal outcome ($\text{SCr} \leq 120\%$ of baseline value) after median 110 months
Tamirou [34]	80	Subgroup analysis of [33]. Different sets of response criteria based on a range of cut-offs of	63.8%	Sensitivity 71% and specificity 75% for favorable long-term (7 years) renal outcome ($\text{SCr} \leq 1.0$ mg/dl).

UPr, SCr, and RBCs at 3, 6, and 12 months. Best
criterion was UPr <0.7 at 12 months

Table 2. Validation of published definitions of disease remission against outcomes in SLE (studies with $n \geq 70$ patients).

* Proteinuria (UPr) assessed by 24-hr urine collection and/or urine protein-to-creatinine ratio

§ $n = 71$ out of 130 with available records

Abbreviations: CRR, complete renal remission (or response); UPr, proteinuria; SCr, serum creatinine; GFR, glomerular filtration rate; CrCl, creatinine clearance; RBCs, red blood cells; HR, hazard ratio; ESRD, end-stage renal disease; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index SLICC group damage index; SAlb, serum albumin; IST, immunosuppressive treatment; HCQ, hydroxychloroquine; N/D, not described.

Specific agreement was also achieved on the definition of “serological activity” where it was agreed that there was sufficient support in the literature pertaining to the presence of anti-DNA antibodies and/or hypocomplementemia (defined as above or below the upper limit of normal value for the local laboratory, respectively), but without reference to other autoantibodies. The task force discussed whether definitions of remission should distinguish patients who are serologically active from those who are serologically inactive, as the former are much more likely to experience subsequent flare.[4, 9] No consensus was reached on that statement and the task force suggested to test each of the clinical criteria with and without serology, in order to determine the usefulness of the latter and whether it adds to the construct validity of each definition.

Finally, there was consensus in the task force that treatment with anti-malarials does not preclude the patient from being considered to be in remission, even though it is somewhat paradoxical to say “off-treatment” when someone is, in fact, taking a medication. However, this step was strongly supported by the task force in respect of the widely-held view that anti-malarials are often considered long-term maintenance therapy for patients with SLE even if they have achieved remission. Benefits of such treatment are believed to extend beyond flare prevention and disease control, and it was therefore felt incorrect to imply that these medication should be discontinued. The task force does recognize that antimalarials have immunomodulatory effects, and that therefore studies done on patients in remission “off treatment” (by the above definition) may in some instances have to distinguish clearly between those patients who are and who are not taking antimalarials. This would perhaps seem most important for studies of an immunological or pathophysiological nature. A similar arguments does of course also apply to medications that do not fall in the above categories but that have or may have immunomodulatory properties, such as statins and vitamin D.

It was also agreed upon by all that patients who are treated with moderate- or high-dose glucocorticoids cannot be considered to be in remission, even if they would fulfill other criteria for

remission. The main argument for this is the well-established adverse health consequence of long-term moderate- to high-dose glucocorticoid treatment.

Two statements were felt to be uncontroversial by the steering committee but did not achieve >90% agreement in the larger task force. One of these, “A definition of remission in SLE must be reasonably consistent with the use of this term in the literature” was intended by the steering committee as indicating that a definition of remission must be aligned with what historically has been considered to be a remission. However, this statement was felt to be a bit too circular by some, given that the literature is divided on the definition of remission.

The statement “Durability in time can be added to any definition of remission in order to define a ‘durable remission’ – but need not be included in the definition of remission itself.” achieved 86% agreement by pre-meeting electronic voting. Notably, although a few of the published definitions included in Table 2 have incorporated a “duration” component (ranging from 6 months to 5 years), the majority to the studies has not examined the prognostic importance of duration of remission against long-term patient outcomes. When discussed face-to-face by the full task force, an increasing number of delegates were unable to support this statement. After discussion, the vote was 65% in favor – not sufficient to declare consensus. The main arguments for and against this statement, as they were discussed during the meeting, are given in **Table 3**:

In favor of the original statement	Against the original statement
(i.e., the definition of remission does <i>not</i> have to include the duration)	(i.e., the definition of remission <i>does</i> have to include the duration)
<ul style="list-style-type: none"> • Definitions of remission in other autoimmune diseases, including 	<ul style="list-style-type: none"> • As SLE can be remitting-relapsing,[37] for a patient to be in remission at one

rheumatoid arthritis [35] and Crohn's disease,[36] do not include durability	specific point in time may not be clinically relevant
<ul style="list-style-type: none"> • Including durability in the definition itself would severely limit the use of the definition as an outcome in clinical trials • Duration can always be added to the analyses in which the definition is used 	<ul style="list-style-type: none"> • Remission for only a short period of time has little relevance in SLE

Table 3. Arguments for and against the statement “Durability in time can be added to any definition of remission in order to define a ‘durable remission’ but need not be included in the definition of remission itself.”

The framework for a definition.

The task force discussed what form a definition of remission in SLE should take. A literature search on this topic identified many observational studies and clinical trials that used a large number of different *ad hoc* definitions of remission in general SLE (Appendix Table 1) and in lupus nephritis (Appendix Table 2). After extensively reviewing various options, and with particular attention to the discussion described above regarding duration, the following three key principles were agreed upon (summarized in **Table 4**):

Key principles for defining remission in SLE		Agreement
1.	• Definitions of remission in SLE will be worded as follows: <i>Remission</i>	93%

	<p><i>in SLE is a durable state characterized by</i></p> <p>(reference to symptoms, signs, routine labs)</p> <ul style="list-style-type: none"> ○ Requirement for serology may be added 	(2 abstained)
2.	<ul style="list-style-type: none"> ● For defining remission in SLE, a validated index must be used <ul style="list-style-type: none"> ○ Suggested indices are: clinical SLEDAI = 0; BILAG 2004 D or E only; clinical ECLAM = 0 ○ These must be supplemented by the Physician's Global Assessment being below an appropriate threshold (e.g., <0.5 on a 0–3 scale) 	98%
3.	<ul style="list-style-type: none"> ● A distinction will be made between remission off therapy and remission on therapy <ul style="list-style-type: none"> ○ Remission off therapy requires the patient to be on no other treatment for SLE than maintenance antimalarials ○ Remission on therapy allows patients to be treated with maintenance antimalarials, stable, low-dose glucocorticoids (e.g., prednisone ≤ 5 mg/day), maintenance immunosuppressives and/or stable (maintenance) biologics 	100% (3 abstained)

Table 4. The task force's three key recommendations for defining remission in SLE.

1. The task force achieved consensus (93%) for the principle that remission in SLE will be defined using the following format:

“Remission in SLE is a durable state characterized by (followed by a reference indicating the absence of symptoms, signs or abnormal labs)”.

It can be recognized that this definition is to some extent a compromise because it does not specify the length of time during which a remission would have to be sustained in order to qualify. This is a direct result of the fact that no agreement on this could be achieved and that the task force felt that further scientific studies are needed to define the optimal duration for any statement of remission in SLE. A further area of uncertainty was whether the absence of active serology would be required and yet again it was felt that this could be investigated in the future. It should therefore also be recognized that ‘abnormal labs’ in the above statement refers to routine laboratory assessments and not necessarily to anti-DNA antibodies or complement levels.

2. The task force spent much time on finding correct formulations for defining the absence of clinical signs and symptoms for use in a definition and agreed, in the end, that for this a validated index must be used (98% agreement). The task force specifically suggests that the following can be considered: clinical SLEDAI = 0; BILAG 2004 D or E categories only; or clinical ECLAM = 0. Furthermore, it is recommended that each of these indices is supplemented with the requirement for the Physician’s Global Assessment (PhGA) to be below a certain level: in the case of a PhGA ranging from 0 to 3 that should be < 0.5. Note that in all instances the term “clinical” for SLEDAI and ECLAM refers to symptoms, signs and routine laboratory testing and disregarding only the points that can be given for the presence of anti-DNA antibodies and/or low complement. The task force also discussed the possibility of defining remission in terms of specific symptoms and signs, such as was done for the proposed definition of remission in pediatric SLE, where certain symptoms and signs are “allowed” for patients with SLE who are nevertheless considered to be in remission.[38] Although a minority of participants favored this

approach, there was a more widespread feeling that *not* using validated indices would to some extent be retrograde, and that practice in various research settings would also increasingly be dominated by the use of such indices.

3. The task force recommends that a distinction should be made between “remission off therapy” and “remission on therapy” (100% agreement). These two descriptors were chosen in preference to many other suggested terms, some of which are: “complete” versus “partial” remission; “complete” versus “clinical” remission; “remission” versus “lupus under control” or “inactive disease”. *While there are subtle nuances differentiating between these possibilities, it was considered important to simplify this matter and to strictly limit the number of definitions to two levels of remission.*

In this regard, it is also important that “off-therapy” will mean that the patient is on no other immunomodulatory treatment for SLE than possibly anti-malarials. As pointed out earlier, for some studies, in particular mechanistic investigations, the immunomodulatory properties of antimalarials must be considered, and in general accurate recording of all medications is recommended.

“Remission-on-therapy” will allow some, but not all medications. Specifically, stable immunosuppressives, including biological immunomodulators, are allowed within this level of remission. It was noted that definitions of remission in other autoimmune diseases, including rheumatoid arthritis[35] and Crohn’s disease[36], do not exclude the chronic use of specific antirheumatic medications, immunosuppressives, or biologics. Likewise, these definitions do not limit the use of glucocorticoids. However, in SLE a major contributor to long-term damage and other adverse outcomes is the chronic use of glucocorticoids, and the task force felt that for the patient to be declared in “remission-on-treatment” the highest allowable dose of glucocorticoids

is 5 mg/day prednisone (or equivalent). Prednisone dose thresholds associated with protection from treatment-related harm are currently being studied by several groups and data from those studies should further inform the selection of a threshold glucocorticoid dose in a definition of remission-on-therapy.

Further development of the most appropriate definition of remission. The task force discussed in what manner a future definition of remission in SLE could be most thoroughly established.

It was agreed upon by voting that for testing the construct validity of each potential remission definition the most appropriate outcomes are death, damage, lupus flares, and HR-QOL measures (100% agreement).

Thus, the task force indicated that any definition of remission in SLE must be tested in terms of the degree to which it correctly identifies patients whose future disease course will be better in these four outcomes. Though mortality remains a key outcome, it is unlikely that many studies will be able to identify this as a differentiating factor. Damage as measured by the SLICC damage index (SDI) [39] will most likely be the most effective way of ascertaining the construct validity of a definition of remission, as has been provisionally demonstrated for the definition of LLDAS. However, the occurrence of flares, especially severe flares, that can be measured by a variety of instruments,[40-42] and measures of HR-QoL will also be important in determining which potential definition of remission in SLE has the greatest validity.

Other points of discussion.

Patient's Global Assessment. There was controversy about the role of the Patient's Global Assessment (PGA) in a remission definition. A majority felt that PGA cannot currently be included

pending further research, and specifically that such research is needed to validate PGA as an outcome in reference to remission. Many felt that a better instrument to capture the patient's perspective may be needed. However, patient representatives (authors KL, CC, BvL) were concerned that the patient perspective was omitted. Indeed, in the T2T recommendations for SLE, both overarching principles and specific recommendations advocate including the patient's perspective in decision-making. However, there is no fully validated measure for the patient's perspective at this time. It was remarked that the PhGA can reflect patient perspective, and it was proposed to emphasize that PhGA should pay careful attention to patient symptoms, or conversely, that PGA could be a longer-term outcome used in the testing of remission definitions; but in formal votes no consensus was reached on these points.

Inclusion of validated skin score. The dermatologists in the task force (authors AK and VPW) suggested to supplement the definition of remission with a validated skin score.

Definition based only on symptoms. A rheumatologist (author MW) pointed out that in as much as the task force is developing *possible* definitions of remission, a definition based only on symptoms and *without* the use of an index could also be tested.

Plans for further work and research agenda. The task force agreed upon a plan of work that would include the use of longitudinal datasets from clinical trials, observational studies, registries etc. to test each of the definitions of remission. Likewise, definitions of remission “on treatment” and “off treatment” will be tested separately against the pre-specified dependent outcomes indicated above, and different durations of these definitions will also be tested. Moreover, studies done on patients “off treatment” will also record the use of antimalarials and analyze the extent to which this makes a difference. As always, findings in such subanalyses may inform future changes in the proposed definitions.

Proposed durations to be analyzed include 6 months, 12 months, 2 years, and 5 years.

In addition to this continued work, the task force also recommends specific research to investigate whether definitions of remission are applicable irrespective of genetic backgrounds and/or ethnicity.

Discussion

An international task force consisting of patient representatives and specialists in clinical immunology, dermatology, nephrology and rheumatology was convened and achieved high-level agreement on eight statements, three key principles, and a set of outcomes relating to remission in SLE, thereby providing a road-map for further work towards a generally applicable definition.

Remission was approached as a global state, whereas it is recognized that remission can be defined, and has in some instances been defined, at the individual organ system level.

As a conceptual starting-point remission was identified as a desirable outcome for patients with SLE with at the very least the absence of major symptoms and signs of SLE. Remission is considered distinct from a cure and it is also regarded as meaningfully different from a state of low disease activity in SLE such as the lupus low disease activity state (LLDAS) that has recently been developed by the Asia-Pacific Lupus Collaboration.[5] However, the latter definition does not solely *require* the presence of low disease activity and does therefore, in fact, include both patients who have a low level of disease activity and also those who are in remission.

Perhaps most critically for future work in this area, it is recognized that remission has to be a state that, if sustained, is associated with a low likelihood of adverse outcome.

Regarding treatment, there was consensus that treatment with antimalarials does not preclude the patient from being considered to be in remission, in respect of the recommendation that anti-malarials should be considered as long-term maintenance therapy for patients with SLE even if they

have achieved remission.[3] It was also agreed upon by all that patients who are treated with moderate- or high-dose glucocorticoids cannot be considered to be in remission even if they would fulfill other criteria for remission. It is well established that glucocorticoids may suppress signs of disease, but will not achieve *bona fide* disease control, and also constitute one of the major risk factors for negative outcomes in SLE.

In contrast to these areas of agreement, no consensus could be achieved on two important issues.

First, it transpired that the inclusion of ‘duration’ in a definition of remission was controversial. Some argued that definitions of remission in other disease areas do not have this requirement, and that utility of a definition in clinical studies including clinical trials will be significantly limited if duration is explicitly required. Others argued that remission achieved on only one given point in time lacks clinical relevance in a disease that can be relapsing and remitting. Following lengthy discussion, the task force was able to agree on a compromise using the wording “Remission is a durable state characterized by” and also clearly identified the need for studies linking the duration of any definition of remission with longer-term outcomes.

Second, the task force did not agree on the precise role of the Patient Global Assessment (Patient GA) in a remission definition. This issue was debated at considerable length. Several task force members including patient representatives were concerned that the patient perspective was not explicitly included in the definition, and emphasized the importance of a definition of remission that ‘resonates’ with the patient. However, a majority of the task force felt that while the patient’s perspective is critically important in the patient-physician interaction, when it comes to a definition of remission for the purposes of clinical and epidemiological studies and clinical trials more work is needed in order either to validate Patient GA as an outcome, or more likely to develop a better instrument to capture the patient’s perspective. It was pointed out that the physician, when assessing disease activity, is expected to weigh in the patient’s perspective.

Additionally, the task force agreed on the definition of “serological activity” but no consensus was reached regarding whether the latter should be taken into account to define remission. The task force agreed upon the use of longitudinal datasets to determine whether serology adds to the construct validity of each definition.

Nomenclature for remission in SLE was extensively discussed. Many terms were proposed, including “complete remission”, “partial” remission”, “clinical remission”, “serological remission”, “lupus under control”, “inactive disease” etc., many of which were overlapping. In order to simplify matters and achieve consistency the task force recommends that only one distinction is made between “remission off therapy” and “remission on therapy”, where “off-therapy” must mean that the patient is on no systemic treatments for SLE other than anti-malarials. While “remission-on-antimalarials-only” would be the most accurate term for this state, “remission off-therapy” was chosen for brevity and convenience, even though it does allow antimalarial therapy. As stated previously, it will be necessary in future studies to account for the actual use of antimalarials in this group of patients, and subsequent analyses of patients who are and who are not on antimalarials may lead to further distinctions in these categories.

“Remission-on-therapy” will allow stable immunosuppressives, including biologics, and low-dose glucocorticoids. It is of interest to note that the latter type of definition is the more usual in other autoimmune diseases, such as RA and Crohn’s disease, and would also allow investigators to use the definition in clinical trials.

One limitation of the approach taken by the task force is the decision to limit serological activity to anti-DNA antibodies and low complement. Recent research shows the importance of antibodies to RNA binding proteins (RBPs) to the formation of immune complexes that can stimulate interferon production. Further research may show that, unless these antibodies are assayed, the serological assessment is incomplete.

Finally, the task force recommends a clear research agenda of testing the construct validity of potential remission definitions against death, damage, lupus flares, and HR-QOL measures as outcomes (dependent variables) in suitable cohorts of patients. Several task force members have conducted or are conducting such studies. This approach will establish which definition(s) of remission in SLE optimally identifies patients with a better disease course in these four outcomes.

In summary, a set of statements and key principles relevant to remission in SLE were established by an international task force. This work provides a pathway for testing individual definitions against longer-term outcomes in order to arrive at a definition of remission in SLE.

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